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21 July, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
rm. 1061
Rockville MD 20852

Dear Sir/Madam

Docket No. 98N-0608

Revision of Requirements Applicable to Albumin (Human), Plasma Protein Fraction (Human) and Immune Globulin (Human)

Please find enclosed two copies of comments on the Food and Drug Administration, Department of Health and Human Services amendments to the specific biologics regulations applicable to blood derivative products [Docket No. 98N-0608].

Yours sincerely

Xenia Sango

Ms Xenia Sango
Regulatory Affairs Manager

98N-0608

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Docket No. 98N-0608

PART 640-ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Subpart H-Albumin (Human)

640.81 Processing

Amendment C. Clarification of Process for Heat Treatment

The regulation is to be amended from:

'(f) *Heat treatment.* Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling. Heat treatment shall be conducted so that the solution is heated for not less than 10 or more than 11 hours at an attained temperature of 60°±0.5°C.'

to

'(f) *Heat treatment.* ***Heat treatment shall be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of 60±0.5°C.'

The proposed amendment should be broadened to allow for heat treatment to occur in bulk during the manufacturing process by deleting/amending the first sentence. The benefits of bulk pasteurization over terminal pasteurization include:

- better control of the pasteurization process, a more rigorous control of temperature and the homogeneity of the product is ensured through mixing, as compared to the reliance on convection heating for pasteurization in the final containers
- improved monitoring of the temperature of the product during pasteurization, as monitoring of product in final containers is difficult, with a reliance on the monitoring of the water bath
- there is no need to maintain a water bath if the product is pasteurized in bulk, therefore there is a reduction in the potential for contamination of the manufacturing facility as water baths are vulnerable to contamination
- the potential for contamination due to moisture accumulation between the stopper and the seal is removed when the need for pasteurization in the final container is removed
- pasteurization in bulk can occur in a less reactive environment (stainless steel tanks) than the product is exposed to when it is pasteurized in the final container which is glass, as glass is more reactive e.g. there is the potential for the leaching of aluminum
- pasteurization in bulk (prior to dispensing), allows for a product that is already Post-VI to pass through the dispensing machines, thereby enabling maintenance of a Post-VI dispensing suite.

In conclusion, given the benefits of bulk pasteurization it is recommended that the amendment enable this inclusion to be proposed.

Amendment D. Clarification for Stabilizer Used in Albumin (Human)

The regulation is to be amended from:

'(f) *Stabilizer.* Either 0.16 millimole sodium acetyltryptophanate, or 0.08 millimole sodium acetyltryptophanate and 0.08 millimole sodium caprylate shall be added per gram of albumin as a stabilizer.'

to

'(f) *Stabilizer.* Either 0.08 ± 0.016 millimole sodium caprylate, or 0.08 ± 0.016 millimole sodium acetyltryptophanate and 0.08 ± 0.016 millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value for the protein concentration of the product as referred to in 640.84(d).'

In terms of the level of sodium caprylate added per gram of protein it is proposed that the concentration range either be increased to allow higher concentrations of caprylate per gram of protein, or the statement be broadened to 'sodium caprylate at a suitable concentration'.

Caprylate and acetyltryptophanate act to stabilize the albumin molecule via interactions with the molecules fatty acid binding sites (Yu & Finlayson, 1984). The caprylate molecule is the more effective binder to these sites and hence a more effective stabilizer, as reflected in the ranges outlined above and in previous studies in which it was demonstrated that one caprylate molecule has the equivalent stabilizing effect as 4 molecules of acetyltryptophanate (Yu & Finlayson, 1984). Additionally, it has been demonstrated in a series of studies conducted by CBER (Division of Blood and Blood Products) scientists, that the albumin denaturation temperature is further increased as the caprylate concentration is increased above 0.08 ± 0.016 millimole sodium caprylate per gram of protein (Ross *et. al.*, 1984; Shrake *et. al.*, 1984; Shrake & Ross, 1988, 1992; Ross & Shrake, 1988). This effect is presumably due to a larger proportion of the fatty acid binding sites on the albumin molecule being occupied by caprylate at any one time.

It ~~has been~~ estimated by Shrake and co-workers that caprylate is able to bind to at least 10 sites on the surface of albumin, of which 8 are thought to be significant (Shrake & Ross, 1988). Thus, by increasing the caprylate range from 0.08 ± 0.016 millimole to 0.16 ± 0.024 millimole per gram of protein provides an increased number of caprylate molecules are able to interact with the fatty acid binding sites. In fact, by using a caprylate concentration of 0.16 ± 0.024 millimole per gram of protein enables 10.5 molecules of caprylate to be present for each albumin molecule ensuring that all potential binding sites are saturated. In comparison, the caprylate concentration of 0.08 ± 0.016 millimole per gram of protein results in 5.25 molecules of caprylate being present for every albumin molecule. As a result, at any one time-point there is an uneven distribution of caprylate molecules bound to the albumin molecules resulting in subpopulations with altered thermal stability properties. Therefore, it is preferable to add an increased concentration in order to ensure that the entire population of albumin molecules exhibit a similar thermal stability profile i.e. 0.16 ± 0.024 millimole caprylate per gram of protein.

Caprylate is a naturally occurring eight-carbon fatty acid, which will be easily metabolized in vivo, and the additional quantity infused will not be expected to have any adverse effect. Support for this conclusion can be obtained from the lack of adverse reactions associated with caprylate in albumin (human) preparations manufactured outside the United States that use higher levels of caprylate 0.1-0.2 millimole caprylate per gram of protein.

In conclusion, it is recommended that the guidelines be altered to enable the inclusion of Albumin (Human) preparations with higher levels of caprylate (0.1-0.2 millimole caprylate per gram of protein) than are currently being proposed in the amendment.

References:

1. Ross PD, Finlayson JS, Shrake A. Thermal stability of human albumin measured by differential scanning calorimetry. II. Effects of isomers of N-acetyltryptophanate and tryptophanate, pH, reheating, and dimerization. Vox Sang. 1984;47:19-27.
2. Ross PD, Shrake A. Decrease in stability of human albumin with increase in protein concentration [published erratum appears in J Biol Chem 1988 Nov 15;263(32):17203]. J.Biol.Chem. 1988;263:11196-202.
3. Shrake A, Finlayson JS, Ross PD. Thermal stability of human albumin measured by differential scanning calorimetry. I. Effects of caprylate and N-acetyltryptophanate. Vox Sang. 1984;47:7-18.
4. Shrake A, Ross PD. Biphasic denaturation of human albumin due to ligand redistribution during unfolding. J.Biol.Chem. 1988;263:15392-9.
5. Shrake A, Ross PD. Origins and consequences of ligand-induced multiphasic thermal protein denaturation. Biopolymers 1992;32:925-40.
6. Yu MW, Finlayson JS. Stabilization of Human albumin by caprylate and acetyltryptophanate. Vox Sang. 1984;47:28-40 (abstr).

Subpart J-Immune Globulin (Human)

640.102 Manufacture of Immune Globulin (Human)

Amendment H. Revision of General Requirements and Sterilization and Heating for Immune Globulin (Human)

Part (e) of the regulation is to be amended from:

'(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45°C and after sterilization the product shall not be exposed to temperatures above 30 to 32°C for more than 72 hours.'

to

'(e) *Sterilization and Heating.* ***after sterilization the product shall not be exposed to temperatures above 32°C for more than 72 hours'

The proposed amendment should be broadened to include other amendments to this section for increased clarity. The first sentence needs to be clarified. It would be useful to define the terms 'final product', and 'after solution' and the approximate timeframe defined by 'promptly'. The second sentence does not seem to allow for pasteurization of the product at elevated temperatures for viral inactivation, therefore it is recommended that the amendment also incorporate this possibility.

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